R.C. (2005). Trends Plant Sci. *10*, 397–406.

Gutiérrez-Marcos, J.F., Costa, L.M., Dal Prà, M., Scholten, S., Kranz, E., Perez, P., and Dickinson, H.G. (2006). Nat. Genet. *38*, 876–878.

Klose, R.J., and Bird, A.P. (2006). Trends Biochem. Sci. *31*, 89–97.

Lippman, Z., Gendrel, A.V., Black, M., Vaughn, M.W., Dedhia, N., McCombie, W.R., Lavine, K., Mittal, V., May, B., Kasschau, K.D., et al. (2004). Nature *430*, 471–476.

Rollins, R.A., Haghighi, F., Edwards, J.R., Das, R., Zhang, M.Q., Ju, J., and Bestor, T.H. (2006). Genome Res. *16*, 157–163.

Saze, H., Scheid, O.M., and Paszkowski, J. (2003). Nat. Genet. *34*, 65–69.

Tompa, R., McCallum, C.M., Delrow, J., Henikoff, J.G., van Steense, L.B., and Henikoff, S. (2002). Curr. Biol. *12*, 65–68.

Tran, R.K., Henikoff, J.G., Zilberman, D., Ditt, R.F., Jacobsen, S.E., and Henikoff, S. (2005). Curr. Biol. *15*, 154–159.

Wilson, G.G., and Murray, N.E. (1991). Annu. Rev. Genet. *25*, 585–627.

Zhang, X., Yazaki, J., Sundaresan, A., Cokus, S., Chan, S.W.-L., Chen, H., Henderson, I.R., Shinn, P., Pellegrini, M., Jacobsen, S.E., and Ecker, J.R. (2006). Cell, this issue.

Caspase-1 Builds a New Barrier to Infection

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Caspase-1 promotes both the maturation of proinflammatory cytokines and apoptosis in cells infected by certain pathogens. Work by Gurcel et al. (2006) now reveals a surprising new function for caspase-1: the stimulation of membrane biogenesis to repair damage caused by bacterial pore-forming toxins. Thus, caspase-1 may promote host cell survival as a means of resistance to pathogenic bacteria.

Pathogenic microorganisms depend on their host for existence. They have evolved strategies to invade, multiply, and propagate within their host while attempting to evade its defenses. Among the weapons at the disposal of pathogens are toxins that form pores in the host cell plasma membrane, which allow the pathogen to inject virulence factors required for infection. Likewise, the host has evolved the means to sense the presence of a pathogen and react to it. These host responses include the activation of an innate immune response and apoptosis. In this issue of *Cell*, van der Goot and colleagues (Gurcel et al. 2006) report a new strategy for host defense in which caspase-1 promotes cell survival by activating a pathway that repairs the cellular damage inflicted by pore-forming toxins.

Inflammatory caspases are central to the host cell response to intracellular pathogens. The best characterized of these is caspase-1. Caspase-1 is activated within the inflammasome, a macromolecular complex assembled by members of the NOD-LRR family of proteins in response to "danger signals." These signals, which are most commonly bacterial products or alterations in the intracellular ionic milieu, appear to act in a specific manner inducing the assembly of specialized inflammasomes. Recently, the stimuli and ligands that activate the NALP3 and IPAF inflammasomes have been investigated. Bacterial RNA (Kanneganti et al., 2006), uric-acid crystals (Martinon et al., 2006), and a decrease in intracellular K^+ levels (Mariathasan et al., 2006) are all known to activate signaling through NALP3, resulting in activation of caspase-1. IPAF, on the other hand, appears to act differently by recruiting caspase-1 in response to bacterial flagellin (Franchi et al., 2006; Miao et al., 2006; Molofsky et al., 2006; Ren et al., 2006). Upon activation, caspase-1 processes the proinflammatory cytokines IL-1β and IL-18, leading to their secretion, which contributes to the innate immune response and host defense. Caspase-1 is also required for the induction of apoptosis in macrophages by certain bacteria.

Gurcel et al. (2006) report a new role for caspase-1 in activating sterol regulatory element binding proteins (SREBPs) to promote lipid biogenesis. The authors studied pathogenic bacteria that secrete protein toxins, which form ion-permeable pores in the plasma membrane of host cells, leading to K^+ efflux. They show that this ionic perturbation is sensed not only by the NALP3 inflammasome but also, surprisingly, by the IPAF inflammasome, leading to caspase-1 activation. The activation of caspase-

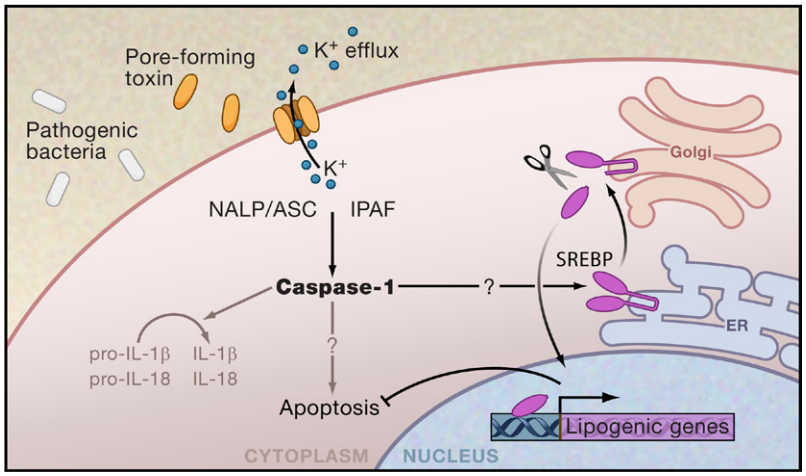

Figure 1. Caspase-1 Mediates Multiple Cellular Responses to Infection
Caspase-1 is at the center of the cell's response to infections and its decision to live or die. Pore-forming toxins from pathogenic bacteria cause K^+ efflux. This "danger signal" is sensed by the NALP3 and IPAF inflammasomes that activate caspase-1. In addition to its effects on the maturation of proinflammatory cytokines and apoptosis, caspase-1 promotes cell survival by activating SREBPs, which switch on lipid metabolic pathways necessary for repairing damage caused by the toxin.

1 within these inflammasomes stimulates the SREBP pathway (Figure 1).

SREBPs are endoplasmic reticulum (ER) membrane-bound transcription factors that function predominantly in cholesterol and fatty-acid biosynthesis. In response to cholesterol depletion, SREBPs exit the ER in COP-II-coated vesicles and are transported to the Golgi apparatus, where they are proteolytically processed by two Golgi proteases. These cleavage events liberate the SREBP transcription domain, which enters the nucleus and acts on target genes to switch on lipid metabolic pathways. Although SREBPs are regulated principally by cellular cholesterol levels, they are also activated by other stimuli such as depletion of ER Ca^{2+} stores or exposure of cells to hypotonic media. Indeed, Gurcel and colleagues (2006) found that bacterial-toxin-induced K^+ efflux triggered SREBP activation and that this was inhibited when cells were cultured in media containing high levels of K^+. Caspase-1 was required for SREBP activation, as downregulation of caspase-1 or downregulation of both NALP3 and IPAF blocked SREBP activity. These observations are important because they not only link ion homeostasis with the activation of lipogenic genes but also identify caspase-1 as a new determinant of lipid metabolism.

However, in response to pathogenic bacteria, cells are faced with the decision to live or die. What then are the effects of caspase-1 activation and lipid metabolism on cell fate? The authors show that blocking caspase-1 by a variety of methods, such as with a selective inhibitor of group I caspases (YVAD) or by siRNA-mediated knockdown of inflammasome components including caspase-1 itself, resulted in higher levels of cell death in response to pore-forming toxins. Similarly, inhibition of the SREBP pathway by trapping SREBP in the ER, blocking its processing at the Golgi, or treating the cell with 25-hydroxycholesterol (25OH Chol), a known inhibitor of SREBP activation, was detrimental to cell survival. These findings demonstrate an essential role for SREBPs and lipid metabolism, downstream of caspase-1 activation, in the resistance of the cell to pathogenic bacterial toxins and in its ability to survive.

The work by Gurcel and colleagues (2006) suggests that caspases play a much more diverse role than previously assumed. In addition, it reveals a role for caspase-1 in cell survival. These findings echo other recent studies demonstrating nonapoptotic functions of caspases (Launay et al., 2005). Caspase-8, for instance, is needed for T lymphocyte survival, proliferation, and activation and was recently reported to regulate cell motility under nonapoptotic conditions. Similarly, *Drosophila* ICE (DrICE) functions in spermatid individualization, and degradation of DIAP1, a caspase inhibitor, does not trigger apoptosis as would be expected but impacts on actin reorganization and cell morphology and differentiation (Kuranaga et al., 2006). In all cases, the questions that remain revolve around whether the catalytic activity of caspases is required for their nonapoptotic functions. If so, what are the substrates that mediate these functions, and what are the mechanisms by which a cell survives in the presence of an activated caspase? SREBPs do not appear to be direct caspase-1 substrates, and the mechanism by which caspase-1 activates them remains unknown. Moreover, our knowledge concerning the role of caspase-1 in apoptosis is limited, as we still do not know how it executes cell death. It is conceivable that caspase-1 acts directly on cellular substrates essential for cell integrity. Alternatively, by processing its cytokine substrates, caspase-1 might be creating an inflammatory environment that feeds back on the cell and contributes to its demise. Because the latter possibility could not have been examined in CHO or HeLa cells, the cells used by the authors, we still do not know whether the survival function ascribed to caspase-1 is cell-type specific. It would be interesting to examine this question in macrophages, the primary cells involved in the defense against invading microorganisms. The question is then whether caspase-1-deficient macrophages are more susceptible to death in response to bacterial pore-forming toxins or K^+ efflux. Recent studies have suggested that, in macrophages, stimuli that lead to pro-IL-1β processing by caspase-1 do not necessarily induce apoptosis and certain inflamma-

somes are needed for IL-1β maturation, whereas others are involved in caspase-1-dependent cell death. Would some inflammasomes activate caspase-1 more efficiently than others? Or do certain complexes inhibit the secretion of active caspase-1 to the extracellular space? Do higher levels of active caspase-1 inside the cell result in a broader spectrum of substrate processing, leading to apoptosis? Finally, during infections, how much can lipids protect us? The authors show that, when using live bacteria instead of pure recombinant pore-forming toxins, cells underwent apoptosis, albeit at lower levels than when lipid metabolism was blocked by an inhibitor of SREBP activation. Do lipids slow down the death caused by invading pathogens and provide the cell with a survival window, giving it time to secrete proinflammatory cytokines, repair itself, and resist the infection? And is it only when the infection is persistent that the cell maintains caspase-1 in a hyperactivated state and commits suicide? Answering these questions will significantly enhance our understanding of the multifaceted roles of caspase-1 in host defense.

REFERENCES

Franchi, L., Amer, A., Body-Malapel, M., Kanneganti, T.D., Ozoren, N., Jagirdar, R., Inohara, N., Vandenabeele, P., Bertin, J., Coyle, A., et al. (2006). Nat. Immunol. *7*, 576–582.

Gurcel, L., Abrami, L., Girardin, S., Tschopp, J., and van der Goot, F.G. (2006). Cell, this issue.

Kanneganti, T.D., Ozoren, N., Body-Malapel, M., Amer, A., Park, J.H., Franchi, L., Whitfield, J., Barchet, W., Colonna, M., Vandenabeele, P., et al. (2006). Nature *440*, 233–236.

Kuranaga, E., Kanuka, H., Tonoki, A., Takemoto, K., Tomioka, T., Kobayashi, M., Hayashi, S., and Miura, M. (2006). Cell *126*, 583–596.

Launay, S., Hermine, O., Fontenay, M., Kroemer, G., Solary, E., and Garrido, C. (2005). Oncogene *24*, 5137–5148.

Mariathasan, S., Weiss, D.S., Newton, K., McBride, J., O'Rourke, K., Roose-Girma, M., Lee, W.P., Weinrauch, Y., Monack, D.M., and Dixit, V.M. (2006). Nature *440*, 228–232.

Martinon, F., Petrilli, V., Mayor, A., Tardivel, A., and Tschopp, J. (2006). Nature *440*, 237–241.

Miao, E.A., Alpuche-Aranda, C.M., Dors, M., Clark, A.E., Bader, M.W., Miller, S.I., and Aderem, A. (2006). Nat. Immunol. *7*, 569–575.

Molofsky, A.B., Byrne, B.G., Whitfield, N.N., Madigan, C.A., Fuse, E.T., Tateda, K., and Swanson, M.S. (2006). J. Exp. Med. *203*, 1093–1104.

Ren, T., Zamboni, D.S., Roy, C.R., Dietrich, W.F., and Vance, R.E. (2006). PLoS Pathog. *2*, e18.

A One-Sided View of Kinetochore Attachment in Meiosis

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Meiosis includes a reductional division in which homologous chromosomes, rather than sister chromatids, are segregated to opposite poles of the spindle. In this issue of *Cell*, Petronczki et al. (2006) report that casein kinase 1 contributes to this process by promoting the attachment of both kinetochores of a homolog to only one pole of the meiotic spindle in budding yeast.

When proliferating cells divide, kinetochores—proteinaceous structures that form on the centromeres of sister chromatids—are captured by microtubules emanating from both spindle poles (bipolar attachment). This bipolar attachment ensures that sister chromatids are faithfully segregated to daughter cells: a process called equational division (Figure 1). During meiosis, however, one round of DNA replication is followed by two rounds of cell division, which results in four daughter cells, each with half the number of chromosomes. The first round of cell division, meiosis I, is characterized by the fact that homologous chromosomes, and not sister chromatids (that are observed in mitosis and meiosis II), are segregated to opposite poles of the spindle. During this "reductional" division, sister kinetochores are always attached by spindle microtubules that originate from the same pole (monopolar attachment; Figure 1). A key question that remains is how monopolar attachment occurs at the kinetochore in meiosis I. In this issue of *Cell*, Petronczki et al. (2006) address this question